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Potential Role of Vitamins and Zinc on Acute Respiratory Infections Including Covid-19

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Abstract

Background. Vitamin C, E, D, A, zinc are considered to be essential in preventing and treating of acute respiratory infections (ARI) including COVID-19. *Methods.* We reviewed published studies evaluating the potential roles of these vitamin and zinc for ARIs and COVID-19 using Medline database, medRxiv, and bibliographic references. *Results.* Vitamins C, D, and E did not reduce incidence of common cold in general, but vitamin C reduced by half in population with physical and environment stresses. Vitamins C and E shortened duration and reduced severity of common cold. A large-dose vitamin A had no effect on recovery from pneumonia. Zinc improved clinical deterioration and pneumonia duration in under five. The effect on preventing COVID-19 morbidity and related-death was lacking. *Conclusions.* Although the effects of vitamins and zinc on ARIs including COVID-19 were inconclusive, taking these for a short period during pandemic may be beneficial when there is risks of deficiency.

Keywords

vitamin, zinc, respiratory infections, COVID-19

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Introduction

Acute respiratory infections remain a major public health problem globally. It may manifest as a mild and self-limited condition such as common cold, or as a severe lower respiratory infection of pneumonia. Common cold is caused by viral infection, which is one of leading causes of doctor visit in US.[1] It also contributed to increase the number of days that people lost in school or work since common cold can occur 2 to 4 times/year in adults and 6 to 10 times/year in children.[1] As a result, this creates common cold as a relatively high cost disease and potentially having less productivity. Pneumonia, which etiology can be viral or bacterial, is the leading cause of morbidity and mortality in young children worldwide. It was reported that pneumonia caused about 11.9 million hospital admissions and 935 000 deaths in 2013 globally.[2,3] A systematic review of 45 community based studies found that the number of episodes of pneumonia in children decreased by 22% from 178 million in 2000 to 138 million in 2015 worldwide. More than 54% of all global pneumonia cases in 2015 were contributed by India, Nigeria, Indonesia, Pakistan, and China. During the Millennium Development Goal period (2000-2015), global hospital admissions for child pneumonia increased by almost 3 times with a more rapid increase observed in the WHO South-East Asia Region than the African Region.[4]

Nowadays, Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), is a major contributor to the global health problem.[5] The range of clinical manifestations of COVID-19 is wide, from asymptomatic to a severe and life threatening disease. It has been identified that angiotensin-converting enzyme 2 (ACE-2) is a receptor for the entry of SARS-CoV-2 into the cell. ACE-2 is expressed in cells in many human organs, by which the clinical manifestations of COVID-19 may

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vary, but the most common symptoms relate to respiratory problems.[6]

Up to now, no proven effective preventive and curative medicine for COVID-19 and other viral acute respiratory infections are available, and therefore, a good immune system is considered to be one of the important measures to prevent the morbidity and mortality related to COVID-19. There are several vitamins and trace elements that have been considered to be essential for the functionally normal immune system particularly vitamin A, C, D, and E, and zinc.[7,8] In this review, we discuss a wide range of evidence related to vitamins A, C, E, D, and zinc and their effect in preventing and treating of acute respiratory infections including common cold, pneumonia, and COVID-19. We aimed to collate information on the role of vitamins and zinc for respiratory infections including COVID-19 and the need of vitamins and the mineral zinc supplementation where possible from the available studies.

Methods

Relevant published literature was initially retrieved by electronic searching in Medline database using predefined keywords: ((vitamin OR "vitamin D" or "vitamin C" OR "vitamin E" OR "vitamin A" OR micronutrients OR zinc) AND ("COVID-19" OR "COVID" OR "SARS-CoV-2" OR "coronavirus" OR "SARS" OR "MERS cov" OR "common cold" OR pneumonia OR "respiratory infection*")).

We initially started with a broad search on the possible effect of vitamins on respiratory infections and further refined the search according to a particular vitamin and COVID-19. Bibliographies of the retrieved articles and medRxiv were further traced to manually obtain additional relevant articles. The search was focused on studies involving pediatric populations and adults. Only publications that at least had abstract in English were included, but we did not limit the publication year.

Ethical Approval and Informed Consent

The ethics committees did not require ethical approval and informed consent because the study based on review of published or publicly reported literature.

Vitamin C and E

Vitamins C and E, as antioxidant nutrients, has been shown to play a role in all human immune systems including epithelial barriers, innate immunity, and adaptive immunity. Vitamin C and E plays a role in collagen synthesis required for stabilization of epithelial barriers.[9] An adequate immune response can also be obtained by maintaining cell integrity, in which antioxidant enables to protect cell from reactive oxygen species or ROS.[10] These antioxidant nutrients also have indirect antioxidant capacity to enhance other substrates that have benefit as antioxidant.[10]

Vitamins C and E also play a role in the regulation of the differentiation, maturation, and function of cells of the innate immune system. Vitamin C has an effect on phagocytic function and lymphocyte cells.[11] Vitamin C may stimulate leukocyte functions, especially of neutrophil and monocyte movement.[11] The effect of vitamin C and E on the immune system can also be explained by increasing the number of lymphocyte proliferation, and rising in interferon production that has an antiviral infection role.[12] Vitamin C is a co-factor that speeding up the hormone production and immune potentiation including its effect on the anti-viral immune responses through the production of interferon-a/b at the initial stage of influenza A virus (H3N2) infection.[13]

Vitamin C and E deficiency has been considered to impair adaptive immune system both humoral and cellular immunity.[14] These involves in the regulation of the proliferation of B- and T-cell differentiation and interaction as well as the balance of T helper cell type 1 (Th1) and T helper cell type 2 (Th2).[9]

Role of Vitamins C and E on Respiratory Infections

Vitamin C deficiency is prevalent in low- and middle-income countries both in children and adults.[15] Based on their advantages in improving human host resistance to infectious disease especially in respiratory infection, vitamin C and E were considered to be effective in reducing the risk, the duration and the severity of respiratory infections.[10,16]

Previous studies on the effectiveness of vitamin C and E on respiratory infections showed varied results. On the one hand, vitamins C and E had significantly proven to reduce lung damage in animals,[17] and the similar result was obtained in elderly.[18] On the other hand, vitamins C and E had no benefit in children who suffered from pneumonia.[12]

There have been many studies evaluated the effects of these vitamins in the incidence, duration and severity of common cold, both as prevention or treatment.[19] Consuming vitamin C did not prevent of having this disease,[7] even in heavy physical activity people.[23] Another study also emphasized that large dose (more than 500 mg/day) and low dose (less than 500 mg/day) of vitamin C consumption did not alter the risk of developing common cold.[20] A systematic review involving 29 trials and 11 306 participants was conducted to determine the effect of vitamin C for the prevention of a cold. In the general population trials involving 10 708 participants showed that regular consumption of vitamin C did not prevent the development of common cold.[19] It means that the risk of suffering from common cold among the people who took vitamin C supplement is similar with the people who did not take it. However, in people who had been exposed with physical and environment stresses such as marathon runners, skiers, and soldiers that consumed vitamin C, their incidence of getting a cold was reduced by half.[19]

With regards to the duration of the disease (mean days of relieving symptoms from common cold or of suffering from this ailment), when was consumed for prophylactic supplement, vitamin C might shortened the duration of common cold of 14% in children and 8% in adults.[19] In children, high dose vitamin C (1-2 g/day) shortened the duration of common colds by 18% and decreased almost a half day per colds duration.[21]

Despite evidences of beneficial effects of regular supplementation of vitamin C on reducing the duration and severity of the disease, it is not reasonable to recommend this in the general population. People have to consume it at least 200 mg/day through the year in reducing a half day of the illness duration from 7 to 10 days of having this disease in general.[19] It certainly does not have a significant clinical benefit and not a cost effective approach in daily practice. However, vitamin C may be more beneficial for those who exposed to a heavy physical activity. Moreover, there are many considerations that should be taken in relating to many factors, which can modify the effect of vitamins C on the common cold. For example, the proportion of dietary intakes of these vitamins, a wide range of dose supplementation, different definitions of study outcomes, and the level of exertion among research subjects.[19] Further, a high dose of vitamin C (3-6 g/day) even though it is safer, it had adverse effects such as having symptoms of upset stomach and diarrhoea.[22]

Limited studies have shown the effect of vitamin E supplementation on the incidence of infectious diseases including respiratory infections. The studies were mostly conducted in elderly. Supplementation of vitamin E had no significant effect on the incidence or duration of both upper and lower respiratory infections.[23] A study among adults aged 50-69 years and smokers showed that vitamin E supplementation increases the risk of pneumonia with body weight less than 60 kg and over 100 kg.[24] Further, vitamin E supplementation also did not lower respiratory tract infections in elderly nursing home residents.[25] In addition, a randomized controlled trial found that consuming vitamin E along with vitamin C more than 90 mg/day has a higher possibility of suffering from tuberculosis.[26]

Possible Role of Vitamin C and E on COVID-19

The supplementation of vitamin C may be beneficial for those with severe COVID-19 who requiring ICU.[27] A meta-analysis of 12 trials with 1766 patients in ICU revealed that vitamin C shortened ICU stay by 8%.[28] Another meta-analysis of 8 trials found that vitamin C shortened the duration of mechanical ventilation in patients who required the longest ventilation.[27] Further, the level of vitamin C was low in critically ill patients.[28,29] A case series of 17 COVID-19 patients who were requiring 30% or more fraction of inspired oxygen (FiO2) showed that supplementation intravenous vitamin C of 1 g every 8 hours significantly decrease the inflammatory markers and FiO2 requirements.[30] Nevertheless, qualified published randomized control trials (RCTs) on vitamin C for COVID-19 were not available at this moment.

Vitamin D

In recent years, vitamin D has received significant attention for the potential roles beyond calcium homeostasis and bone metabolism. A number of studies have documented evidence that vitamin D had a strong linkage to immune system, both for infectious diseases and non-infectious problems such as malignancy, cardiovascular and autoimmune diseases.[31,32]

In infectious diseases, vitamin D plays a role in preserving physical barrier of the immune system through maintaining mucosal junction integrity, which is commonly disturbed by virus and other microorganisms.[31,32] Vitamin D enhances innate and cellular immunity partly through the induction of antimicrobial peptides, including human cathelicidin and LL-37. Cathelicidin directly exhibits antimicrobial activities, enveloped and nonenveloped viruses, and fungi.[33] Further, LL-37 reduces influenza A virus replication.[34] The expression of antimicrobial peptides is crucial in protecting the lung from infection.[35]

In the adaptive immune response vitamin D suppresses pro-inflammatory cytokines mediated by the T helper cell type 1 (Th1) and up-regulates anti-inflammatory cytokines production by the T helper type 2 (Th2) cells.[36] Furthermore, calcitriol or 1,25-dihydroxy vitamin D3 promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes.[37]

Role of Vitamins D on Respiratory Infections

Vitamin D deficiency are common in children, even in those living in settings with abundant sun exposure.[38-40] A systematic review of vitamin D status worldwide involving 195 studies from 44 countries with 168 000 subjects found that vitamin D deficiency was prevalent among adults and elderly as well.[41]

Despite strong evidences of the important role of vitamin D on the immune system, clinical trials showed inconsistent findings for the effect of vitamin D supplementation on respiratory infections. A systematic review, which included 39 studies (4 cross-sectional studies, 8 case-control studies, 13 cohort studies and 14 clinical trials), showed significant associations between low vitamin D status and increased risk of both upper and lower respiratory tract infections from observational studies.[42] Nevertheless, conflicting results were reported from RCTs.[42]

Possible Role of Vitamin D on COVID-19

A recent published study conducted in European countries revealed that mean level of vitamin D in each country was negatively correlated with the number of COVID-19n cases/1 million as well as the mortality/1 million. Further, vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland, which is the most vulnerable group of population for COVID-19.[43] However, this might be influenced by the effect of meteorological factors on the spread of COVID-19 such as temperature or humidity.

In patients with COVID-19, the innate immunity might produce both pro-inflammatory and anti-inflammatory cytokines in response to the viral. Vitamin D might also enhances cellular immunity partly by reducing the cytokine storm.[44]

Vitamin A

As a barrier function, vitamin A has an effect on epithelial integrity with the formation of the epithelium, epithelial keratinization, stratification, differentiation, and functional maturation of epithelial cells.[45] In innate immunity, vitamin A plays a role in regulating the differentiation, maturation, and function of macrophages and neutrophils in order to enhance killing and phagocytosis.[46] Vitamin A has effects on humoral immune response by immunoglobulin production and B-cell regulation. On cellular immune response, vitamin A may induce T cell migration and regulate T-cell production.[46]

Role of Vitamin A on Respiratory Infections

Vitamin A is regarded to enhance immune function and functionally regulate cellular and humoral immune responses.[46] Vitamin A supplementation to children aged 2 to 8 years who were vitamin A and D insufficient has been proved to enhance immune response to influenza virus vaccination.[47]

A high dose of vitamin A supplementation reduced the severity and the duration of pneumonia as well as their mortality in children with measles.[48] However, another study found that there was no beneficial effect of vitamin A supplementation on severe pneumonia in children.[49] A systematic review involving 5 studies and 2177 children found that large-dose vitamin A had no effect on the recovery from pneumonia in children aged less than 6 years in low- and middle-income countries.[50]

Possible Role of Vitamin A on COVID-19

No published studies specifically evaluated the effect of vitamin A on preventing and treating COVID-19. A recent study evaluated the potential therapeutic targets and mechanisms of vitamin A for the treatment of COVID-19 using a network pharmacology method. They found that the mechanisms of action of vitamin A against SARS-CoV-2 include the enrichment of immunoreaction, inhibition of inflammatory reaction, and biological processes related to reactive oxygen species.[51]

Zinc

Zinc is an essential trace element which plays a role in enhancing immune system. Deficiency of zinc can impact immunity because it maintains barriers and develops both innate and adaptive immune systems. Zinc deficiency leads to lack of formation, activation and maturation of lymphocytes, disturbs the intercellular communication via cytokines, and weakens the innate host defence.[52,53] Zinc deficiency may impair phagocytosis of macrophages and neutrophils, NK cell activity, generation of the oxidative burst and complement activity.[54] Zinc deficiency also reduce lymphocyte proliferation, Th1 cytokines production (IL-2 and interferon-γ), and leads to a Th1/Th2 imbalance.[55] Not only having an effect on cell-mediated immunity, zinc is also an anti-inflammatory and antioxidant agent.[56] Zinc is also considered to be a second messenger in immune cells. Its role includes activating T cells by the T cell receptor and the cytokine interleukin IL-2, and antibody-binding receptors which are predominantly found on cells of the innate immune system.[57]

Role of Mineral Zinc on Respiratory Infections

Zinc deficiency is a public health problem, which was common particularly in Sub-Saharan Africa and South Asia.[58] In children, zinc deficiency has been associated with an increased risk of respiratory tract morbidity. A randomized controlled trial study among 103 children aged 1 month to 5 years with pneumonia evaluated the

Table 1. Synergetic Mechanisms of Vitamin C, D, E, A, and Zinc on Immune System.

Immune system	Vitamin C	Vitamin D	Vitamin E	Vitamin A	Zinc
Barriers	Collagen synthesis for stabilization of epithelial barriers	Maintenance of mucosal junction integrity, proliferation or maturation of keratinocyte, formation of permeability barrier in the skin	Collagen synthesis for stabilization of epithelial barriers	Formation and protection of epithelium and mucus integrity (epithelial keratinization, stratification, differentiation, and functional maturation of epithelial cells)	Cellular proliferation (thickness maintenance)
Innate immunity	Stimulate leukocyte functions, stimulate neutrophil and monocyte movement, protect neutrophils against ROS- induced damage, improve chemotaxis, enhance killing and phagocytosis, enhance production of interferon	Improve chemotaxis and phagocytic capabilities, produce antimicrobial proteins (defensin β2, cathelicidin, LL-37), modulate cytokine, induce regulatory T cells	Stimulate leukocyte functions, protect neutrophils against ROS- induced damage especially of neutrophil and monocyte movement, enhance killing and phagocytosis, enhance production of interferon	Regulate the differentiation, maturation, and function of macrophages and neutrophils, enhance killing and phagocytosis	Enhance phagocytosis of macrophages and neutrophils, activate Natural Killer cell, generate the oxidative burst, activate complement, modulate cytokine
Adaptive immunity	Regulate the proliferation of B- and T-cell differentiation and interaction	Regulate the proliferation of B- and T-cell differentiation and interaction	Regulate the proliferation of B- and T-cell differentiation and interaction, balance of Th1 and Th2	Regulate the proliferation of B- and T-cell differentiation and interaction including induce T cell migration	Regulate the proliferation of stem cells, B- and T-cell differentiation and interaction, balance of Th1 and Th2

effect of zinc supplementation on the duration of illness, respiratory rate and oxygen saturation. This study showed a statically significant clinical improvement in the zinc supplemented group compared to placebo.[59] Further, zinc supplementation among those who zinc deficiency prevents respiratory morbidity especially in children in a low-to-middle-income countries.[60] Zinc also reduced the duration of fever and the severity of illness in boys with severe pneumonia.[49]

Possible Role of Zinc on COVID-19

There was no published studies specifically evaluated the effect of zinc on preventing and treating COVID-19. However, an invitro study found that zinc may have antiviral activity to inhibit SARS-CoV RNA polymerase. Therefore, zinc may have a beneficial effect on COVID-19 infection.[61]

Implications for Patient Care

Based on those aforementioned explanations, the synergistic mechanisms of vitamin C, E, D, A, and zinc in immune system particularly in respiratory infections exist. The potential mechanisms of vitamins and zinc in immune functions are summarized in Table 1. Further, the prevalence of deficiency of these vitamins and zinc are common worldwide both in adults and children. This review found that vitamins and zinc may be associated with the prevention and reduction of respiratory infections from the available published studies.

Alternative approaches in preventing and treating the respiratory infections including common cold, pneumonia and COVID-19 including an adequate level of vitamins C, E, A, and D that can be obtained from natural dietary intake and a standard precaution for the acute respiratory infections that can be implemented in daily life. For example, vitamin C can be easily found in broccoli, citrus fruit, and tomatoes; whereas vitamin E can be found in seeds, nuts, oils, and cereals.[62] Other sources of vitamin D can be obtained from the diet as vitamin D2 or vitamin D3 such as oily fish, egg yolks and fortified foods.[63] Further, deficiency of vitamin D might be common even among those living in country where sun exposure is abundant as reduced sun exposure due to increased sedentary activities or sequestered in lipocytes among obese population. Therefore, physical activity and adequate sun exposure, eating foods that naturally contain vitamin D or are fortified with vitamin D might provide vitamin D sufficiency.

The common cold as well as other upper respiratory infections is mostly caused by virus, which is a self-limited disease. Based on pathophysiologic point of view, this ailment can be relieved by their adequate immune systems, which normal people commonly have. Thus, another way to prevent common cold is that surely by preventing a direct transmission, which allows virus from infected spread to susceptible individuals.[64] It can be achieved by frequently hand washing with plain soap (non-antimicrobial soap) and water at least 60 seconds because it can eradicate the virus completely. Alternatively, they suggest using alcohol containing hand disinfection that was much easier, had less time hand washing of 20 seconds, and also had a maximum reduction in viral load. Cutting fingernails, which had much resident micro flora that generally was neglected in, should also be regularly done. In addition, and people that suffer from common cold should covering their nose and mouth when coughing, promptly disposing used tissue, and using mask to limit spread infection. Finally, keeping space for at least 2 m can prevent suffering from common cold because droplet that contains many viruses from respiratory tract infection might not suspend for an extended period, and it can transmit to others if they are in less than 1 m space from an infected patient, which is known as human-to-human transmission.

In addition to basic hygienic practices aforementioned above, proper dietary and lifestyle behaviors are essential for prevention and treatment of respiratory viral diseases, such as COVID-19. Everyone including self-quarantine patients need to follow food based dietary guidelines. These include consuming at least 5 portions of fruit and vegetables each day and all main meals should contain adequately proportional amount of carbohydrate, fat, and protein rich foods on a daily basis.[65] When there is risks or signs or symptoms of vitamin deficiency, taking multivitamin, and mineral supplement for a short period during this pandemic may be beneficial.[65]

Conclusion

Vitamin C, D, E, A, and zinc have potential roles on the system immune. However, the effects on acute respiratory infections including common cold, pneumonia and COVID-19 were inconclusive. Vitamins C, D and E do not reduce the incidence of common cold in general population, but vitamin C may reduce by half in people who are exposed with physical and environment stresses. Even though vitamins C and E can shorten the duration and reduce the severity of the disease, it is not reasonable to consume them regularly in order to having a minimal reduction in clinical setting application. A large-dose vitamin A had no effect on the recovery from pneumonia in children. Zinc supplementation may improve the clinical deterioration and the duration of pneumonia in children under five. A body of evidence on the effect of these vitamins and mineral zinc on preventing COVID-19 morbidity and COVID-19 related death was lacking. It might be beneficial to consume a variety of natural foods that contain those vitamins, do physical activity with sensible sun exposure, and prevent respiratory infections by using a standard precaution to limit the spread of infection such as hand washing, using mask, and keeping distance.

Author Contributions

All authors contributed to the conceptualization and methodology of the study. IKM searched and selected the studies, and wrote the first draft of paper. IKM, EPP, and RT reviewed and edited the manuscript before submission. All authors approved the final submitted version.

Declaration of Conflicting Interests

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